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WHAT'S NEW IN INTENSIVE CARE

Vasopressor use in septic shock: separating evidence, practice, and future directions

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Vasopressors are cornerstone therapies in septic shock, aimed at restoring mean arterial pressure (MAP) and preserving organ perfusion. Current international guidelines recommend norepinephrine as first-line therapy [1], with the addition of non-catecholaminergic vasopressors when needed to reach arterial pressure targets while limiting catecholamine exposure [2]. Despite its apparent simplicity, this stepwise approach implicitly assumes that distinct vasopressor pathways can be meaningfully mobilized at the bedside, even though clinicians currently lack real-time, patient-specific biological information to guide such decisions.

This commentary aims to clarify the current state of vasopressor use in patients with septic shock by deliberately separating three levels of reasoning: what is supported by existing evidence, what clinicians pragmatically do in daily practice despite uncertainty, and how future research could better inform individualized therapy. The objective is not to redefine recommendations, but to provide a transparent framework that aligns clinical decision-making with the realities and limits of current knowledge.

What we currently know

Current evidence on vasopressor use in patients with septic shock highlights a clear separation between what is established, what is assumed mechanistically, and what remains uncertain (Table 1).

What clinicians pragmatically do in daily practice despite uncertainty

Clinicians initiate norepinephrine early as first-line therapy in patients with septic shock, consistent with current recommendations [2]. As catecholamine doses increase, the risk of dose-related adverse effects, particularly pro-arrhythmic and ischemic complications, also increases. In this context and given the absence of clear evidence supporting one approach over another, two pragmatic strategies are commonly adopted in daily practice: either increasing norepinephrine alone or adding vasopressin as an add-on to limit further catecholamine exposure.

When vasopressin is considered, it should probably be introduced relatively early in the course of septic shock, rather than reserved for late or refractory shock [5]. Importantly, a careful reassessment of the hemodynamic profile is required before adding a second vasopressor. Persistent preload dependence or sepsis-induced myocardial dysfunction should be screened, as hypotension in these settings may not primarily reflect vasoplegia.

Angiotensin II cannot currently be recommended as part of routine vasopressor strategies.

Hydrocortisone consistently reduces norepinephrine requirements [10] and should be considered in patients in situations of high norepinephrine doses. This likely reflects the ability of corticosteroids to improve vascular sensitivity to catecholamines by upregulating adrenergic receptors, decreasing pro-inflammatory activity that contributes to vasoplegia, and by correcting relative adrenal insufficiency. In addition, sedative agents may exert vasodilatory or myocardial depressant effects that in turn increase catecholamine requirements. Minimizing sedation can, therefore, reduce catecholamine exposure and potentially decrease the risk of adverse effects.

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Table 1 Vasopressor use in patients with septic shock: current evidence and uncertainties

	Current clinical practice	Putative mechanism	Available evidence	Remaining uncertainties
Norepinephrine	Norepinephrine is recommended at first-line in patients with septic shock [2]. Dose is titrated to achieve MAP targets.	α-adrenergic vasoconstriction increasing systemic vascular resistance. Increased venous return leading to higher cardiac preload.	Has the strongest evidence base in septic shock. No defined dose–response threshold, with marked interindividual variability [3, 4]. High doses are associated with proarrhythmic and ischemic adverse effects.	Interindividual variability in pharmacokinetics and vascular responsiveness is not measurable at the bedside and not accounted for in current strategies.
Vasopressin	Vasopressin is either not initiated or is suggested as an add on vasopressor when norepinephrine requirements reach a predefined threshold, commonly between 0.25 and 0.5 µg/kg/min (norepinephrine base) [2]. It is typically added to norepinephrine, with the primary aim of achieving target MAP while limiting further catecholamine escalation. Strategies for vasopressin discontinuation vary widely, and tapering practices are empirical.	Relative deficiency of endogenous vasopressin during septic shock or impaired non-adrenergic vascular tone. Addition of vasopressin is assumed to restore vascular tone through V1-receptor-mediated vasoconstriction and to reduce catecholamine exposure by allowing norepinephrine dose reduction.	Randomized trials have not demonstrated a reduction in overall mortality with vasopressin use in patients with septic shock [5–7]. Subgroup analyses suggest a signal toward lower mortality when vasopressin is introduced at lower norepinephrine doses (e.g., < 15 µg/min norepinephrine base) [5] or earlier during shock evolution. In contrast, initiation of vasopressin at higher norepinephrine doses has not been associated with improved mortality [5]. Evidence for effects on renal outcomes or need for renal replacement therapy remains inconsistent [6].	Addition of vasopressin has not demonstrated clear benefit on clinical outcomes, such as mortality or reduction of renal replacement therapy. The optimal norepinephrine threshold and timing for vasopressin initiation remain uncertain. Personalization of vasopressin therapy based on endogenous vasopressin levels or biomarkers has never been tested at the bedside. Optimal strategies for vasopressin withdrawal, including whether vasopressin or norepinephrine should be tapered first, remain unknown.
Angiotensin	Angiotensin II is not recommended in current practice in patients with septic shock. Its use is authorized as a rescue therapy in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressor support.	Dysregulation of the renin–angiotensin–aldosterone system with relative angiotensin II deficiency. Relative angiotensin II deficiency due to RAAS dysregulation; nonadrenergic vasoconstriction through the AT1 receptor allowing catecholamine sparing.	Angiotensin II increases MAP and reduces norepinephrine requirements but has not shown a mortality benefit in septic shock populations [8]. Post-hoc analyses suggest lower mortality when introduced at lower norepinephrine doses, similar to vasopressin [9].	Studies were not powered for mortality or renal outcomes. Optimal timing, norepinephrine threshold and biomarker-guided use remain undefined.

AT1 receptor angiotensine II receptor type 1, *MAP* mean arterial pressure, *RAAS* Renin–angiotensin–aldosterone system

How future research could better support individualized therapy

Norepinephrine

Norepinephrine use is still largely guided by MAP targets rather than by individual pharmacologic, biological, or physiological responses. For a given dose, plasma norepinephrine concentrations vary widely across patients [3]. Differences in clearance, receptor density or sensitivity, intracellular signaling, and interactions with concomitant therapies contribute to this variability. As a result, dose escalation may reflect reduced responsiveness rather than insufficient exposure, exposing some patients to unnecessary catecholamine toxicity. Future research should aim to move from dose-based escalation toward effect-based strategies, through bedside assessment of norepinephrine exposure, vascular responsiveness, or dynamic testing of adrenergic sensitivity (for example, a MAP test).

Vasopressin

Vasopressin represents a conceptually different approach, targeting a non-adrenergic pathway. In septic shock, circulating vasopressin concentrations initially rise but subsequently decline as stores become depleted, resulting in a progressive relative deficiency [11]. This deficiency is more marked in patients with septic shock than in severe sepsis or sepsis and more marked in septic shock than in cardiogenic shock [12]. Circulating vasopressin concentrations and receptor responsiveness are highly heterogeneous among patients, yet vasopressin is currently introduced in a standardized manner, without real-time assessment of pathway integrity. This may partly explain the neutral results of large trials. Future studies may focus on identifying patients most likely to benefit from vasopressin supplementation using functional or biological markers of vasopressin pathway impairment rather than fixed catecholamine thresholds.

Angiotensin II

Dysregulation of the renin–angiotensin–aldosterone system is common in patients with septic shock but remains highly variable among patients, and hemodynamic responses to exogenous angiotensin II are heterogeneous [13]. While adequately powered trials designed to assess clinically meaningful outcomes such as mortality, renal function, or vasopressor-related complications remain necessary, complementary lines of research are also needed to better characterize this pathway at the individual level.

Several signals suggest that only subsets of patients may experience hemodynamic benefit from angiotensin II [13]. An elevated angiotensin I/II ratio has been associated with higher vasopressor requirements in distributive shock, suggesting a relative endogenous angiotensin II deficiency [14]. In addition, post-hoc analyses indicate a greater MAP response to angiotensin II in patients not exposed to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers [15], further underscoring interindividual variability in treatment response.

Future research may, therefore, prioritize the development of rapid, bedside-accessible tools to assess the activity of the renin–angiotensin–aldosterone axis in real time. Such approaches could enable mechanistic phenotyping and improve patient selection in future trials, helping to distinguish true lack of efficacy from inadequate biological stratification.

The way forward

In current practice, norepinephrine is initiated early as first-line therapy in septic shock. When MAP remains inadequate and catecholamine exposure increases, clinicians pragmatically either continue norepinephrine alone or add vasopressin. If vasopressin is chosen, it should likely be introduced early, after reassessment to exclude persistent preload dependence or sepsis-induced myocardial dysfunction. Hydrocortisone should be considered in patients with escalating norepinephrine requirements, and sedative doses minimized to limit unnecessary vasopressor exposure.

Beyond these pragmatic principles, vasopressor management remains largely guided by dose and arterial pressure targets, despite marked interindividual variability in biological or physiological responses. Neutral trial results for adjunctive vasopressors likely reflect inadequate patient stratification rather than lack of relevant physiological pathways. Progress in septic shock care will depend on developing bedside tools capable of identifying the mechanisms contributing to hypotension in individual patients, enabling a shift toward personalized, mechanism-targeted vasopressor therapy.

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Declarations

Conflicts of interest

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